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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,434	01/10/2002	Jurgen Denecke	9052-84	1446

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,434	DENECKE ET AL.	
	Examin r	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 14-16* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group I (claims 1-5, 7, 10-11, and 14-16) in the paper filed 21 July 2003 is acknowledged. The traversal is on the ground(s) that the inventive concept does not reside in a method of increasing BiP levels but in the consequence of elevated BiP levels, that is, greater pathogen resistance. Applicant urges that Crofts et al is merely an example by which high BiP levels can be achieved, and other methods of over-expression of BiP are possible, as stated in the specification. This is not found persuasive because the claims are not drawn to a method of increasing pathogen resistance but to a method of increasing secretory protein synthesis. Furthermore, any method that increases expression of BiP would inherently increase pathogen resistance. Lastly, one method of over-expressing BiP makes obvious the broad genus of methods of overexpressing BiP. Thus, the method taught by Crofts et al would inherently increase pathogen resistance because the method steps are the same as recited in claim 1, and the method would inherently increase the capacity for secretory protein synthesis.

Claim 9 should have been included in Group I, and will be so examined.

A search on Group I found art on Group II, so the restriction between Groups I and II is withdrawn and both Groups I and II will be examined.

Claim 8 is withdrawn from consideration as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the city and either state or foreign country of residence of each inventor.

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

3. The abstract is not descriptive of the instant invention, which is a method of increasing secretory protein synthesis by transformation with a nucleic acid encoding BiP. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

4. The title of the invention is not descriptive of the instant invention, as above. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Sequence identifiers are missing from pg 3, line 19.

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth herein. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

Claim Objections

6. Claims 2-9, 11 and 14 are objected to because of the following informalities:

Claims 2-9, 11 and 14 start with an improper article.

In claims 2-3 and 5-9, a comma should be inserted after "1".

In claim 4, a comma should be inserted after "3".

In claim 11, a comma should be inserted after "10".

In claim 14, a comma should be inserted after "15".

7. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim fails to further limit the parent claim because any method that increases expression of BiP would inherently reduce the period of time within which the plant's natural defense mechanism responds to attack by a plant pathogen.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-8, 10-11 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the capacity for secretory protein synthesis in a plant by transforming the plants with a nucleic acid that encodes tobacco BiP and plants and plant cells thereby obtained, does not reasonably provide enablement for a method of increasing the capacity for secretory protein synthesis in a plant by overexpressing BiP by any method and plants and plant cells thereby obtained. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of increasing the capacity for secretory protein synthesis in a plant by overexpressing BiP by any method and plants and plant cells thereby obtained.

The instant specification, however, only provides guidance for analysis of BiP (lumenal binding protein) and ß-1,3-glucanase expression in tobacco leaves treated with fungal cell-wall degrading enzymes in both the presence and absence of salicyclic acid (SA) to show that BiP RNA expression is transiently and systematically increased prior to the prolonged glucanase expression (examples 1-2); analysis of BiP expression in tobacco NahG and Arabidopsis sail plants to show that induction of BiP and glucanase expression is SA independent (examples 3 and 11); analysis of BiP expression in plants with increased levels of unfolded proteins (UPR) to show it increases (example 4); production of plants transformed with a nucleic acid encoding BiP and showing that they do not have increased glucanase expression and that in the presence of UPR glucanase expression is decreased (examples 5-6); demonstration that SA induction of BiP occurs prior to induction of PR genes and is not light dependent and that induction is inhibited by cell-wall degrading enzymes and is additive to UPR (examples 7-10); analsyis of PR1 gene expression in plants transformed with a nucleic acid encoding BiP to show that the rate of induction is increased in those plants (example 12); and analysis of secretory protein synthesis to show that increased BiP levels alleviate ER stress (examples 14-16).

The instant specification fails to provide guidance for a method of increasing the capacity for secretory protein synthesis in a plant by overexpressing BiP by any method and plants and plant cells thereby obtained.

The instant specification fails to provide guidance for exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than that encoding tobacco BiP.

The specification fails to teach nucleic acids encoding BiP or calreticulin homologues. The specification also fails to teach the ATPase domain of BiP.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

The specification fails to teach a method of increasing the capacity for secretory protein synthesis in a plant by overexpressing BiP by any method other than transformation with a nucleic acid encoding BiP.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

10. Claims 1-7, 9-10 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a use of a multitude of nucleic acids encoding homologs of BiP or calreticulin. In contrast, the specification only describes a nucleic acid from tobacco encoding BiP. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described nucleic acids encoding homologs of BiP or calreticulin within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997) at pg 1406:

> ... A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.
> ... the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-7, 9-11, and 14-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claim 1 is indefinite in its recitation of "causing". It is not clear what one is doing here.

Claims 1, 3-7, 10-11 and 14-16 are indefinite in their recitations of "homologue". How a homolog differs from BiP and calreticulin, in sequence and in function, is unclear.

Claims 5-7 are indefinite in their recitations of "containing". It is unclear if this word is intended to be open or closed. If open language is intended, the word should be replaced with --comprises--.

Claim 5, line 4, claim 6, line 4, and claim 7, line 6, are indefinite in their recitation of "3' untranslated end". Does Applicant mean a 3' untranslated region or does Applicant mean this is the end of the chimeric gene?

Claim 5, lines 4-4, claim 6, line 5, and claim 7, line 6, are indefinite in their recitation of "stop sequence". Does Applicant mean that the region contains a stop codon or is Applicant referring to something else?

Claim 16 is indefinite in its recitation of "in an amount sufficient to protect the plant". It is unclear what that amount is.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Crofts et al (1998, Plant Cell 10:813-823).

Crofts et al disclose plants transformed with a nucleic acid encoding BiP and plants overproducing calreticulin (pg 816, right column). The plants inherently have increased pathogen resistance. BiP inherently comprises an ER retention signal.

15. Claims 1-4, 10-11 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Arora et al (1998, Physiol. Planta. 103:24-34).

Arora et al teach a method of increasing the capacity for secretory protein synthesis by causing plant to maintain in at least a part of the plant a level of BiP greater than the endogenous level under non-stressful conditions. Arora et al do this by water-stressing the plants (pg 30, left column, paragraph 2). The plants have levels of BiP that are over 5 times that of the endogenous level under non-stressful conditions (Figure 9).

16. Claims 1-4, 10-11 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (1992, Protoplasma 171:142-152).

Zhang et al teach maize mutant plants in which BiP levels are at least five times that of the levels in non-mutant plants (Fig. 3). These plants would inherently have an increased capacity of secretory protein synthesis and would inherently have a reduced response time to pathogen attack.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-7, 10-11 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crofts et al (1998, Plant Cell 10:813-823).

The claims are drawn to a method of increasing the capacity for secretory protein synthesis in a plant by overexpressing BiP and plants and plant cells thereby obtained.

The teachings of Crofts et al are discussed above. Crofts et al do not disclose the constructs used to transform the plants and the levels of BiP produced in those plants.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of overexpressing BiP and calreticulin in plants as taught by Crofts et al, to use constructs having a strong constitutive promoter and a 3' termination sequence. One of ordinary skill in the art would have been motivated to do so because the CaMV 35S promoter is the most commonly used promoter in plant molecular biological research and because 3' termination signals are required for correct expression of exogenous genes in

plants. At least some of the transformants would have levels of BiP three or five times greater than the endogenous levels. BiP would comprise the ATPase domain of BiP.

19. Claims 9 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crofts et al as applied to claim s 1-7, 10-11 and 14-15 above, and further in view of Denecke et al (1995, Plant Cell 7:391-406).

The claims are drawn to a method of increasing the capacity for secretory protein synthesis in a plant by overexpressing BiP and further treating the plant with salicyclic acid.

The teachings of Crofts et al are discussed above. Crofts et al do not disclose further treating the plant with salicyclic acid.

Denecke et al teach that the levels of BiP are increased in response to salicyclic acid (Figure 9).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of overexpressing BiP in plants as taught by Crofts et al, to further treating the plant with salicyclic acid as described in Denecke et al. One of ordinary skill in the art would have been motivated to do so to increase the expression of BiP in the plants.

20. Claims 1-4, 6, 10-11 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coughlan et al (US Patent 6,171,864, filed July 1996).

The claims are drawn to methods of increasing the capacity for secretory protein synthesis in a plant by overexpressing calreticulin and plants and plant cells thereby obtained.

Coughlan et al teach plant cells transformed with a vector encoding calreticulin (claims 13-14), which would increase the levels of BiP in the plants over the endogenous levels. Coughlan et al do not disclose plants transformed with a vector encoding calreticulin, wherein the plants have levels of BiP at least three times greater than the endogenous levels.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing plant cells transformed with a vector encoding calreticulin as taught by Coughlan et al, to regenerate those plant cells into plants. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Coughlan et al to do so (column 14, lines 66-67). At least some of the transformants would have levels of BiP three or five times greater than the endogenous levels.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
October 31, 2003